UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,384	12/20/2001	Claude Perreault	5600-74	4899

20792 7590 07/28/2005

MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/028,384	PERREAULT ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 84-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 84, 85, 87-89* is/are rejected.

7)☒ Claim(s) *86* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply filed on 04/28/2005 is acknowledged. Claim 1, 84-89 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The substitute specification filed on 4/28/2005 has been entered. However, the specification is still objected because the specification does not list corresponding SEQ ID NOs for those peptides sequences in Fig. 1, and also at page ~~apge~~48, line 12. The sequence listing has the corresponding SEQ ID NO, for example the triangle at Fig. 1 is SEQ ID NO: 313. Amending the figure legend to include the corresponding SEQ ID NO would obviate this objection. New specification is not required. Applicant is kindly requested to go over the entire specification to check whether there is any other consecutive amino acids sequence bigger than 4 amino acids, and if there is, amend the specification to include the required SEQ ID NO.

Claim Rejections - 35 USC § 112, Maintained

Claim 1 remain rejected, claims 84, 85, 87-89 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecules encoding the three peptides shown in Fig. 1 in vitro use, does not reasonably provide enablement for any other nucleic molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant argues that the cytotoxic assay shows that the peptide 18 works with HAL A2, thus the specification provides sufficient guidance for one of skill. This argument has been fully considered but found unpersuasive because applicant is arguing limitation not present in respect to peptide 18, and applicant's argument is not commensurate in scope of the claims in respect to both the nature of the peptide and MHC molecule. Both the attached Annex 1, and the specification, the guidance is limited to peptide 18, and HLA A2. Note Table 1 of the specification showing there are more than 10 MHC molecules, and guidance with one of them is not seen as sufficient. demonstrate a CTL clone 18.

In response to Sherman of record, and Lauritzen of record, applicant also argues that different peptides from the protein encoded by the claimed nucleic acid have the potential to bind various MHC molecules as shown Table 1, applicant also argues that CTLs with low affinity would not be a problem in context of allogeneic MHC. T cells with low affinity could recognize or a tumor antigen. In addition, in response to the Office's position that clonal deletion in the thymus would lead to the deletion of cells recognizing self-proteins, applicant argues with autoimmune disease, which originates from activation of CTL directed against self-antigens. Applicant also argues with Fujita et al., disclosing an immune response could be generated against the ubiquitously expressed p53 protein.

These arguments along with all the attached supporting documents have been fully considered but found unpersuasive.

Applicant argument with autoimmune disease appears to be arguing a limitation not present in the claims. The claims do not say anything about autoimmune disease. As for argument that clone 18 with HLA A2 works, the argument is considered as not commensurate in scope of the claims because the claims are not limited to those that works.

As for all other arguments, this scope of enablement rejection is maintained based on the interpretation of the claims as drawn to an isolated nucleic acid molecules encoding peptides binding to an HLA antigen and is recognized by cytotoxic T lymphocytes for use in antisense therapy and/or a pharmaceutical. As stated before, Riott et al (Immunology, Fourth Edition, 1996, Mosby, page 7.9-7.11) teach that a foreign protein is entered in a host due to infection or other event such as cancer development in a host, it is broken down into short chains of amino acids known as peptides. The cell then "presents" these cleaved peptides on its surface via a protein known as MHC, which stands for major histocompatibility complex. In this manner, the cell "marks" itself to be destroyed. Special immune system cells known as cytotoxic T lymphocytes (CTLs) then recognize and destroy the marked cells. CTLs are antigen-specific; that is, the introduction of a particular antigen into the body activates specialized CTLs that recognize that antigen. The CTLs then target those cells whose surfaces are marked with a fragment of the activating antigen. T cells recognizes cell-bound antigen in association with MHC molecules. MHC class I and class II act as guidance systems for T cells. This is known as MHC restriction. Only a minority of peptide fragments from a protein antigen is able to bind particular MHC molecules.

Different MHC molecules bind different sets of peptides. Riott et al specifically teach Fig. 7.22 and Fig. 7.23, and also page 7.10, right column that the peptides sizes 12-15 are optimal for MHC molecule class I and certain amino acids at certain positions are critical for binding to MHC class I.

The specification does not establish the biological function of the newly discovered protein, other than disclosing the two peptides (as shown in Fig. 1) fragments from instant SEQ ID NO:2 encoded by SEQ ID NO:1 work as T cell epitopes. The specification does not disclose common structural attributes that stimulate an immune response and binds to one or more MHC molecules presented on the surface of cells. There is insufficient guidance regarding the parameters and sequence of peptides which correlate with the ability to stimulate T cell with any MHC molecule and generate CTLs with claimed specifity/activity. There is insufficient guidance regarding selection of peptides that meet the instant criteria of stimulating T lymphocytes with specific activity. Thus, there is insufficient guidance regarding the parameters and sequences of peptides which correlate with the ability to be recognized by the specific CTL clone.

US Pat. 5,840,839 (Nov. 24, 1998) teach at column 19 that finding a peptide that binds to a MHC molecules and stimulates immune response is not a trivial matter. The '839 patent at column 19, lines 53 to 67 teaches that structure a T cell epitope that stimulates immune response in context of MHC molecules is unpredictable in the current state of art. The '839 patent at columns 19-20, and Table 1 teaches that the various candidate T cell epitopes selected based on theoretical binding motif of one

class of MHC molecule, i.e. HLA-A31 do not work when they are experimentally tested as shown in Table 1. This suggests that theoretically selected T cell binding motifs have to be tested experimentally in order to determine whether they are actually T cell epitopes or not.

The specification provides insufficient guidance with regard to theses issues and provides no working examples of a peptide that would work with any MHC molecule. Considering the state of art, the broad scope of claims in respect to the nature of peptide and also to the nature of MHC molecules, it is concluded that that undue experimentation is required to practice the claimed invention. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Searching potential T-cell epitopes in instant SEQ ID NO:2 using existing software (this use is considered as research, not patentable use) does not require undue experimentation. Undue experimentation is required to use the potential T-cell epitopes as immunogen to illicit anti-tumor response i.e. using as an tumor antigen peptide in a subject. The specification fails to teach how administration of the claimed peptide would produce a sufficient amount of CTLs, to destroy tumor cells expressing SEQ ID NO:2. Cancer therapy using immunogen is still unpredictable in the art. The specification teaches that SEQ ID NO:2 is a self antigen (note the claim construction of 1-3, and 6 for example), rather than a mutated antigen, as it is expressed on normal tissues as well as cancerous tissues and that self-tolerance may eliminate T cells that are capable of recognizing these epitopes with high avidity (Sherman, LA et al, 1998,

Critical reviews in Immunol, 18(1-2): 47-54, see especially at the abstract and Table 2). In other words, only CTLs with low affinity are left, which may not be optimal for tumor elimination *in vivo*. One of the problem is that after some period of time in the presence of tumor cells, T cells may lose their functional activity. Lauritzsen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that a clonal deletion of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD+4 T-cells which are specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD+4+8 and CD+4 thymocytes. This negative selection was specific for the transgenic thymocytes that would complement the idiotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a plasmacytoma which had a different idiotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor cells, caused a profound reduction of the specific thymocytes specific to the idiotype of the plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete of shed antigens. In the instant case, the antigens are known self-antigens. It would be reasonable to conclude that said normal antigens are presented within the thymus to developing thymocytes and T-cells with high affinity for said antigens are deleted as "self". It would be also reasonable to conclude that administration of the claimed polypeptides or cells expressing said polypeptides would not result in an efficacious vaccine as a T-cell response would not

be evoked due to the process of clonal deletion in the thymus, rendering the host devoid of T-cells which are specific to the self-protein. Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regiments comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even thought P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. With regard to the isolation of two T-cells which are specific for the instant antigen presented in the context of HLA-A24, it cannot be determined if this is a reliable indicator that in all patients, with any of the types of cancers listed on page 20, would have a T-cell available after thymic selection which would react with said antigen in the context of HLA-A24 or any other MHC molecule.

The specification does not provided any evidence that any of the vast number of possible potential SEQ ID NO:2 derived T-cell epitopes might be able to be used for cancer therapy. It is concluded based on the references discussed above, that the state

of the art with respect to treating cancer patients of administering tumor antigens is unpredictable. The specification does not provide any disclosure that the administration of the claimed polypeptides would generate CTLs which lyse the cells of a tumor and it cannot be predicted based on disclosure of the specification.

As for new claims 87, 88, the specification has assertion that the claimed nucleic acid being expressed in tumor cells. However, the specification does not teach which protein encoded by a nucleic acid 97 % sequence identity SEQ ID NO:1 or 91 % sequence identity nucleic acid encoding SEQ ID NO: 2 is overepxressed in proliferative cells, or essential for the tumor cell's survival. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Claim 84 is included in this rejection because of the Markush choice of b). The indefinite article "an" in front of "amino acid sequence" is construed as claiming any fragment of protein encoded by an open reading frame of SEQ ID NO:1

Considering the limited guidance, no working examples in the specification, and the unpredictability in the art, it is concluded that undue experimentation is required to use the full scope of the claimed invention. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Claim 1 remain rejected, claims 85, 87-89 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description**

requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are interpreted as drawn to genus of nucleic acid molecules with various of degrees of differences in terms of structures from 97 % sequence identity SEQ ID NO:1 or 91 % sequence identity to nucleic acid encoding SEQ ID NO: 2.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of % identity along with the expression language of "expressed ubiquitously in human cells...potential of generating a plurality of protein fragments binding with high affinity to a human HLA molecule". The expression language recited in the base claim 1 does not appear to be associated with the claimed structures because all of the applicant's provided references for traversing the scope of the enablement rejection above, especially Fujita et al., teach that an unrelated sequence has the same expression pattern as the instantly recited expression pattern. In other words, the recited expression language is not correlated with the claimed partial structures.

In addition, the specification does not teach which protein encoded by a nucleic acid 97 % sequence identity SEQ ID NO:1 or 91 % sequence identity nucleic acid encoding SEQ ID NO: 2 is overepxressed in proliferative cells, or essential for the tumor cell's survival as claimed in the new claims 87, and 88. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 102, Maintained

Claim 1 remains rejected and the new claims 84, 85, and 87-89 are newly rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/25962 (18 June 1998).

Claims 1, 84, 85, and 87-89 are interpreted as drawn to an isolated nucleic acid molecule comprising a fragment of SEQ ID NO:1 or nucleic acid fragment encoding SEQ ID NO:2 (note the indefinate article being used in the claims), wherein the nucleic acid encoding a protein having the potential of generating a plurality of protein fragments binding to high affinity to a human HLA molecule, is expressed ubiquitously in human cells (claim 1), overexpressed in proliferative cells (claim 87), said proliferative cell is tumor cells (claim 88).

WO 98/25962 (18 June 1998) at page 79-81, claim 35 teaches SEQ ID NO: 18, which encodes instant SEQ ID NO: 2 protein from the amino acid #504-826 (note attached Exhibit A), and nucleic acid capable of hybridizing to various fragments of SEQ ID NO: 18, how to use the fragments of disclosed human cDNA in DNA sequencing and hybridization analysis at page 29, as T-cell epitopes at pages 39-44, various reagents

including reaction buffers for detection at page 32, how to make the protein using the expression vector comprising the disclosed cDNA at page 34-35.

WO 98/25962 does not disclose an expression data. However, given 100 % match to C-terminal 322 amino acids of instant SEQ ID NO:2 (note the attached sequence alignment, Exhibit A), especially the nucleic acid encoding the SIMP peptide, with a high affinity binding motif for A-0201 HLA molecule i.e. "LMLLMMFAV" and other sequences (note Table 1 of the instant specification), it appears that the protein encoded by SEQ ID NO:18 of WO 98/25962 inherently has the characteristics specified in instant claims 1-5. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the isolated human nucleic acid molecule of the prior art does not possess the same material, structural and functional characteristics of the instantly claimed nucleic acid molecule. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed nucleic acid molecule is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

Claim 86 is objected because it depends on the rejected base claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642